Reduction of serum 25-hydroxyvitamin D concentrations with intravenous lipid emulsion in a dog

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Abstract — The recommended daily allowance of vitamin D has been increased. Toxicosis in pets may increase as a result. A dog ingested ~ 200 000 IU of vitamin D, serum concentrations were above the reference range (RR) and decreased to the RR after lipid treatment. This is the first known report of lipid treatment for hypervitaminosis D.

Résumé — Réduction des concentrations sériques de 25-hydroxyvitamine D à l'aide d'une émulsion intraveineuse de lipides chez un chien. L'apport quotidien recommandé de vitamine D a été accru. La toxicose chez les animaux de compagnie peut augmenter en raison de cette hausse. Un chien a ingéré ~ 200 000 UI de vitamine D, les concentrations sériques étaient supérieures à la fourchette de référence (FR) et a chuté à la FR après le traitement aux lipides. Il s'agit du premier rapport connu de traitement aux lipides pour la toxicose à l'hypervitaminose D.

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Vitamin D deficiency has recently been associated with increased rates of cancer (1), Alzheimer's disease (2), multiple sclerosis (3), bacterial and viral infections (4,5), inflammation (6), and congestive heart failure (6). As a result of apparently widespread deficiency, new guidelines have been published increasing the recommended daily allowance significantly for adults, children, and infants (7). These guidelines coincide with the widespread availability of high concentration vitamin D supplements, which can be obtained over the counter (8). The potential for acute toxicosis in veterinary patients is likely to increase as a result of this increased exposure.

The physiology of vitamin D has recently been reviewed for veterinary medicine (9,10). Briefly, vitamin D is present in nature in 2 active forms: vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol). Ergocalciferol is found mostly in plant matter while cholecalciferol can be found in the soft tissue of animals. Cholecalciferol can be naturally produced in the mammalian body from the precursor 7-dehydrocholesterol, which is found in the skin and is converted to cholecalciferol when exposed to ultraviolet light in some species. Both ergocalciferol and cholecalciferol can be consumed and rapidly absorbed from the gastrointestinal system and then converted into the active metabolite 1,25-dihydroxyvitamin D (calcitriol) via the kidneys. The highest concentrations of calcitriol are found in the serum 48 to 96 h after vitamin D exposure (10). Calcitriol, in turn, increases calcium absorption in the intestines, mobilizes calcium from the bone, and increases calcium reabsorption from the kidneys resulting in a rise in the serum concentration of calcium and phosphorus. All forms of cholecalciferol are highly lipophilic and therefore can remain in the fat stores within the body for long periods of time with a slow release (11).

Vitamin D intoxication in veterinary patients is most commonly due to accidental ingestion of cholecalciferol containing rodenticides or human medication and dietary supplements (12,13). The clinical signs of cholecalciferol toxicosis are associated with the resulting hypercalcemia and hyperphosphatemia and their detrimental effects on the renal, central nervous, muscular, gastrointestinal, and cardiovascular systems. If left untreated, these patients proceed into acute renal failure and soft tissue calcification. With high level exposures clinical signs can be seen as soon as 12 to 72 h after ingestion (10). Acute ingestion of cholecalciferol-containing products should be medically addressed quickly.

Intravenous lipid emulsions (ILE) are being used with increasing frequency in both human and veterinary medicine to treat acute systemic intoxications ranging from local anesthetic drugs to other lipophilic drug poisonings (14–17). Treatment with ILE has been shown to reverse the cardiotoxic effects of local anesthetic overdose as well as other medications such as beta blockers, calcium channel blockers, parasiticides, herbicides, and a variety of psychotropic agents. As a result, ILE is currently

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Table 1. Serum 25 hydroxyvitamin D concentrations pre- and post-infusion of intravenous lipid

Sample	Result (nmol/L)	Reference range (canine) (nmol/L)
0-minute — before lipid infusion	224	60 to 215
60-minute after lipid infusion	193	60 to 215
120-minute after lipid infusion	143	60 to 215

being used in human resuscitation due to cardiac arrest from unknown drug overdoses when generic first-line treatment has failed.

The owner of a 2 year-old male, castrated Pomeranian-Shih Tzu mix dog, weighing 8.5 kg, reported that she found a bottle of Vitamin D_3 (Nature's Bounty, Bohemia, New York, USA) that had been chewed open and she estimated that 90 to 100 capsules were missing. Each capsule contained soybean oil, gelatin, and vegetable glycerin while providing 2000 IU (50 μg) of cholecalciferol. At the maximum possible consumption, the dog would have ingested 200 000 IU (5000 μg). The owner unsuccessfully attempted to induce emesis by administering oral hydrogen peroxide to the dog and then brought him to the veterinarian the next morning, approximately 12 h after suspected ingestion.

On presentation, the dog's initial physical examination was unremarkable with vital signs all within normal reference ranges. The veterinarian administered 4.5 g of activated charcoal in a 45-mL slurry (Toxiban; Lloyd, Shenandoah, Iowa, USA) by mouth and then drew blood for a serum chemistry profile. Serum was immediately frozen for later evaluation of cholecalciferol concentration. At that time, all values on the serum biochemistry panel were within normal limits except for phosphorus, which was mildly decreased [1.4 mmol/L, reference range (RR): 1.7 to 3.4 mmol/L]. The serum calcium concentration was 2.8 mmol/L (RR: 2.0 to 3.2 mmol/L). Intralipid 20%, (Baxter Healthcare Corporation, Deerfield, Illinois, USA), a 20% intravenous fat emulsion, was administered as a bolus dose of 1.5 mL/kg body weight (BW) given over 15 min and then followed with a constant rate infusion at 0.5 mL/kg BW/min for 30 min. Additional serum samples were taken at 60 and 120 min post-completion of the lipid infusion. The samples were immediately frozen and shipped to the Michigan State University Diagnostic Center for Population and Animal Health for 25-hydroxyvitamin D (25, OH-D3) level analysis. The 25, OH-D3 was measured with a commercially available and validated radioimmunoassay post acetonitrile extraction (DiaSorin 25-Hydroxyvitamin D ^{125}I RIA kit, Stillwater, Minnesota, USA). The assay has 100% specificity for 24, 25-(OH)2-D2; 24,25-(OH)2-D3; 25,26-(OH)2-D2; and 25,26-(OH)2-D3. There is only 0.8% cross reactivity with un-hydroxylated vitamin D.

The patient was placed on IV 0.9% saline after collection of the final serum sample. After 24 h the patient was discharged on a low calcium prescription diet (Hill's KD; Hill's, Topeka, Kansas, USA). The dog was returned 48 h later for recheck biochemistry panel, which was unremarkable aside from an elevated total bilirubin of 37.6 μmol/L (RR: 0 to 15.4 μmol/L). The serum calcium concentration at this time was 2.8 mmol/L. Pre-lipid infusion serum 25, OH-D3 concentrations were above the reference range and decreased into the normal range after lipid infusion. The values were as follows: pre-lipid infusion (224 nmol/L), 30 min post-lipid infusion (193 nmol/L), 60 min post-lipid infusion (143 nmol/L) (RR: 60 to 215 nmol/L).

The dog in this case report could have ingested a maximum amount of 200 000 IU of vitamin D. Hypercalcemia was not evident in the immediate period post ingestion. Since intravenous fluids were not started until after the final serum sample was collected, lipid therapy, which was the only intervention to decrease the serum concentration of vitamin D, is likely to be responsible for the decrease in this case. In addition, the short time frame of the lipid treatment and the slow elimination of vitamin D, make it unlikely that the vitamin D concentration decreased due to normal elimination. Although the dog was treated with activated charcoal before lipid treatment was administered this could only have decreased gastrointestinal absorption, it would not directly reduce serum concentrations of vitamin D.

Hypervitaminosis D, defined as any value of 25, OH-D3 above the reference range, is thought to be a precursor to vitamin D intoxication and may be present in patients with normal calcium concentrations (18). Recently, accidental overdose in an infant was reported with documented ingestion of 240 000 IU of vitamin D without laboratory evidence of hypercalcemia (18). Another report in a child documented accidental ingestion of 2 400 000 IU (600 000 IU/day over 4 d) and this patient presented with hypercalcemia that persisted for 14 d, suggesting that the toxic threshold for vitamin D may be quite high (19).

In recent years, there has been an upsurge in recommendations for higher levels and more frequent oral vitamin D supplementation. Both forms of vitamin D, ergocalciferol and cholecalciferol, are available as manufactured nutritional supplements and have been shown to increase the serum concentration of 25, OH-D3. While it appears that both forms are efficacious, cholecalciferol is considered to be more potent than ergocalciferol, and is therefore 10 times more toxic in humans. It is not clear which form dogs absorb more readily (8).

Most veterinary reports of vitamin D toxicosis involve consumption of cholecalciferol-based rodenticides, erroneous cholecalciferol concentrations in commercial pet food, consumption of human anti-psoriatic medications, or over supplementation of livestock (12,13,20). To the authors' knowledge, this is the first reported case of hypervitaminosis D following consumption of human over-the-counter vitamin D supplements.

Intravenous lipid emulsions have been used with increasing frequency to treat acute systemic toxicities involving local anesthetics and other lipophilic, non-anesthetic drugs. Reviews of recent case reports and uses of intravenous lipid emulsions in veterinary medicine have been recently published (21). Several mechanisms of action have been suggested with the most widely accepted theory based on the idea of a "lipid sink" (21). The increased lipid concentration introduced into the plasma is thought to create a new pharmacokinetic equilibrium which converts the drug from the tissue to the aqueous plasma phase, and then to the lipid phase. Lipophilic substances are attracted to the high concentration of fat and a concentration gradient

forms between the tissue and blood, causing the drug to move away from fat deposits within the body. As a result, we hypothesized that the lipophilic nature of vitamin D would allow the intravenous lipid emulsion to exert the same "lipid sink" effect, thereby decreasing the amount of circulating active drug and reducing toxicity. To the authors' knowledge, this is the first report of hypervitaminosis D treated with intravenous lipid emulsion. Although the dog herein likely ingested a sub-lethal dose of vitamin D the lipid emulsion was able to successfully reduce the serum concentration of 25, OH-D3 quickly. This may point to lipid emulsion as a possible treatment in vitamin D intoxication of unknown or lethal amounts. In most cases of vitamin D ingestion the clinician does not know the serum concentration of vitamin D for at least a week if samples are sent out at all. This can be very frustrating because hypercalcemia may manifest while waiting on vitamin D concentrations. Veterinarians can monitor serum calcium concentrations as a marker of toxicity but waiting until hypercalcemia develops might not be in the best interest of the pet. Future studies should focus on whether early treatment of vitamin D overdose with lipid emulsion prevents the hypercalcemia of vitamin D intoxication. Prevention of the consequences of hypercalcemia could be lifesaving in some animals. As a result of these findings, further consideration should be given to intravenous lipid emulsions in cases of severe, acute cholecalciferol intoxication.

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